JACC Vol. 45, No. 2, 2005
January 18, 2005:318–28

Efficacy of a Patient-Activated Pharmacologic Pump Using Phenylephrine as Active Drug and Prodromal Symptoms as a Marker of Imminent Loss of Consciousness to Abort Tilt-Induced Syncope

To the Editor: An implantable drug-delivery system (DDS) recently has been proposed as a potentially useful treatment for severely symptomatic patients with vasovagal syncope (VVS) (1,2). In the present study, we assessed, during head-up tilt tests (HUTTs), the usefulness of a prototype of a patient-activated DDS that uses phenylephrine as an active agent and prodromal symptoms as a marker of imminent loss of consciousness.

In this single patient-blind, randomized study, each patient underwent two consecutive HUTTs. In one test, a bolus of phenylephrine (1 mg/1 ml) was injected into the right atrium during the time when a VVS developed and blood pressure decreased by more than 50%; in the other, the same volume of placebo (saline solution) was delivered. The study consisted of two phases. During the first phase (physician test), phenylephrine and placebo were injected by the attending physician by means of a syringe. In the second phase (patient test), phenylephrine and placebo were delivered by the patients themselves at the time they experienced prodromal symptoms, by means of a modified version of Algomed pump (Medtronic Inc., Minneapolis, Minnesota) (Fig. 1).

A total of 27 patients with frequently recurrent VVS (median number, 20), were studied (26 women; mean age, 49 years): 17 during the physician test and 10 during the patient test. All patients had a reproducible positive response to at least two baseline HUTTs performed according to the "Italian protocol" (type of positive response: mixed in 11 patients, vasodepressor in 11 patients, and cardioinhibitory in 5 patients). All 27 patients had a positive response during both tilt tests with phenylephrine and placebo injection.

During the physician test (Table 1), the administration of phenylephrine led to an immediate increase in blood pressure in 15 of 17 patients (88%). This increase reversed, a few seconds after injection, prodromal symptoms and prevented syncope in nine subjects (53%) and restored consciousness in six subjects (35%), even though patients continued to be tilted upward at the same angle. In only two patients (12%), both of whom had an asystolic pause >3 s, was phenylephrine injection unsuccessful. Phenylephrine was always well tolerated. The administration of placebo did not prevent or abort syncope in any patient ($p < 0.001$ compared with phenylephrine).

During the patient test, all 10 patients studied were able to activate the DDS appropriately. The delivery of phenylephrine was successful in every subject (efficacy 100%) without the occurrence of side effects. The administration of placebo was not effective in any patient ($p < 0.001$ compared with phenylephrine).

In the physician test, the mean time between onset of symptoms and injection of phenylephrine or placebo did not differ significantly (69 s vs. 58 s). After the injection of phenylephrine, the drug took effect very soon (within 13 ± 7 s), and all patients who recovered consciousness did so within a mean of 32 ± 17 s. The maximum effect of phenylephrine was observed after 90 ± 35 s. Baseline values were restored in approximately 5 min. After the injection of placebo, the mean time of syncope development was 32 ± 23 s; tilting was stopped and patients were returned to the supine position within 50 ± 22 s. In the patient test, a similar timing of the effects of phenylephrine and placebo injection was observed.

All patients experienced premonitory symptoms at the time of VVS. In the physician test, the mean duration of prodromal symptoms was 101 ± 40 s during the test with phenylephrine injection and 90 ± 35 s during the test with placebo injection. In the patient test, the corresponding values were 123 ± 39 s and 96 ± 31 s, respectively.

In our study, phenylephrine proved to be significantly more efficacious than placebo in preventing tilt-induced syncope. The efficacy of phenylephrine, an alpha-agonist agent, was clearly due to its potent vasoconstrictor effect. Indeed, the drug determined an immediate marked increase in blood pressure, which interrupted the VVS, even though the pre-existing reflex bradycardia increased further as a result of baroreceptor activation. Phenylephrine was not able to prevent syncope in only two patients, both of whom had a severe cardioinhibitory response. Phenylephrine was safe and well tolerated in all cases. Moreover, phenylephrine acted very rapidly and had a short action of duration. Thus, phenylephrine seems to be an ideal agent for a DDS for the treatment of VVS.

Other drugs have been evaluated for potential use in a DDS. Ammirati et al. (1) assessed the efficacy of etilefrine, another alpha-agonist agent, and found that it was successful in 87% of cases as opposed to 20% when placebo was injected. In a previous study, Santini et al. (2) observed a 70% efficacy using atropine, a pure anticholinergic agent, versus a 22% success rate using placebo. However, in these two studies, drugs and placebo were administered randomly to different patients and not compared in the same subjects. Moreover, in the Santini et al. (2) study, atropine and placebo were injected during the very initial stage of the neuromediated reflex.

In the present study, we found that, at the time of VVS, all subjects experienced warning symptoms for a reasonably long period of time. This period allowed the subjects to self-activate the DDS appropriately and effectively. These results suggest that prodromal symptoms may constitute quite a valuable marker of incipient VVS and may serve as a "sensor" in a patient-activated DDS.

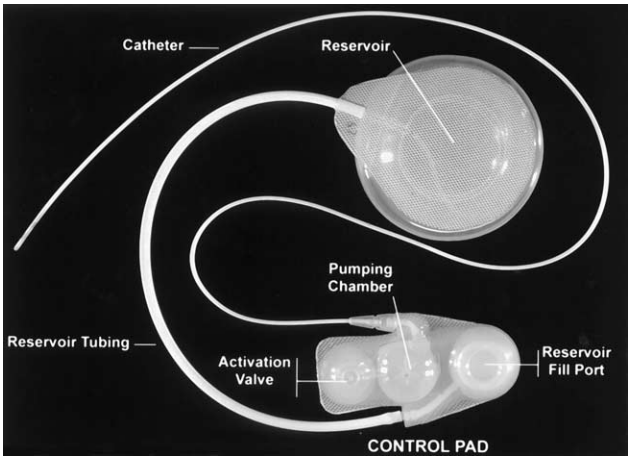

Figure 1. Modified Algomed pump.

Table 1. Blood Pressure and Heart Rate During HUTT With Placebo and Phenylephrine Injection

	Physician Test (n = 15)		Patient Test (n = 10)	
	Phenylephrine	Placebo	Phenylephrine	Placebo
Systolic blood pressure (mm Hg)				
Supine	141 ± 20	129 ± 23	140 ± 16	142 ± 16
Tilting start	144 ± 23	128 ± 24	149 ± 18	144 ± 10
Symptoms onset	105 ± 19	96 ± 21	122 ± 23	106 ± 20
Injection	62 ± 13	61 ± 14	76 ± 16	74 ± 10
End point	121 ± 19*	50 ± 13	116 ± 32*	59 ± 9
Maximum effect	175 ± 35		177 ± 19	
Diastolic blood pressure (mm Hg)				
Supine	73 ± 12	68 ± 14	74 ± 14	73 ± 11
Tilting start	82 ± 14	76 ± 16	87 ± 3	85 ± 6
Symptoms onset	65 ± 12	62 ± 19	78 ± 15	72 ± 11
Injection	44 ± 11	45 ± 14	55 ± 13	51 ± 10
End point	73 ± 10*	37 ± 12	79 ± 20*	39 ± 8
Maximum effect	100 ± 16		102 ± 10	
Heart rate (beats/min)				
Supine	77 ± 16	75 ± 12	72 ± 10	74 ± 13
Tilting start	85 ± 19	93 ± 15	87 ± 11	88 ± 12
Symptoms onset	97 ± 26	97 ± 24	99 ± 21	105 ± 15
Injection	81 ± 30	88 ± 27	96 ± 26	98 ± 22
End point	68 ± 25	75 ± 21	70 ± 21	75 ± 26
Maximum effect	59 ± 21		55 ± 13	

*Phenylephrine vs. placebo: $p < 0.01$ (two-tailed paired Student t test).
End point = syncope or normal state of consciousness; HUTT = head-up tilt test.

Finally, in our study, all patients were able to activate easily the Algomed system at the time of prodromal symptoms, and injection of phenylephrine was effective in every patient. These results indicate that the modified Algomed pump is an efficient prototype of a patient-activated DDS for the treatment of VVS during HUTT. Obviously, our data are experimental, and further studies are needed to confirm these laboratory results in clinical practice.

***Antonio Raviele, MD**
Franco Giada, MD
Gianni Gasparini, MD

*Divisione di Cardiologia
Ospedale Umberto I
Via Circonvallazione, 50
30170 Mestre-Venezia, Italy
E-mail: araviele@tin.it

doi:10.1016/j.jacc.2004.10.020

REFERENCES

1. Ammirati F, Colivicchi F, Santini M. Effects of intravenous etilefrine in neurocardiogenic syncope induced by head-up tilt testing. Am J Cardiol 2000;86:472–4.
2. Santini M, Ammirati F, Colivicchi F, Gentilucci G, Guido V. The effect of atropine in vasovagal syncope induced by head-up tilt testing. Eur Heart J 1999;20:1745–51.

Association of Smoking With Improved Myocardial Perfusion and the Angiographic Characterization of Myocardial Tissue Perfusion After Fibrinolytic Therapy for ST-Segment Elevation Myocardial Infarction

To the Editor: ST-segment elevation myocardial infarction (STEMI) may arise from different pathophysiologic processes ranging from plaque rupture to endothelial surface erosion. In the latter case, exposure of a denuded endothelium to a "high-risk blood phenotype" of elevated procoagulant factors and activated inflammatory cells may be the major trigger for thrombus formation. In particular, cigarette smoking is associated with increases in circulating fibrinogen and tissue factor (1), suggesting that thrombus in smokers with STEMI may be more fibrin-rich and, therefore, more amenable to fibrinolytic therapy.

Despite an increased risk of developing myocardial infarction, smokers with STEMI have a lower mortality compared with nonsmokers. This was first noted in the Thrombolysis In Myocardial Infarction (TIMI)-2 trial and has been largely attributed to fewer comorbidities and younger age among smokers. However, smoking has also been independently associated with lower mortality (2) and with better epicardial flow after fibrinolytic therapy (3). Although we were unable to detect differences in myocardial perfusion among a limited number of patients from older fibrinolytic trials (4), we hypothesized that in a larger population treated with current fibrinolytic therapy, smoking might be associated with improved myocardial perfusion as a potential unidentified explanation of the "smokers' paradox."

Data were drawn from patients in the Integrilin and Tenecteplase in Acute Myocardial Infarction (INTEGRITI), Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction